## AUG 0 2 2004 W

## SEQUENCE LISTING

Zankel et al.

<120> USE OF THE CHAPERONE RECEPTOR-ASSOCIATED PROTEIN (RAP) FOR THE DELIVERY OF THERAPEUTIC COMPOUNDS TO THE BRAIN AND OTHER TISSUES

- <130> 30610/39383
- <140> US 10/600,862
- <141> 2003-06-20
- <160> 28
- <170> PatentIn version 3.2
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- Gln Arg Leu His Leu Pro Pro Val Arg Leu Ala Glu Leu His Ala Asp 35 40 45
- Leu Lys Ile Gln Glu Arg Asp Glu Leu Ala Trp Lys Lys Leu Lys Leu 50 55 60
- Asp Gly Leu Asp Glu Asp Gly Glu Lys Glu Ala Arg Leu Ile Arg Asn 65 70 75 80
- Leu Asn Val Ile Leu Ala Lys Tyr Gly Leu Asp Gly Lys Lys Asp Ala 85 90 95
- Arg Gln Val Thr Ser Asn Ser Leu Ser Gly Thr Gln Glu Asp Gly Leu
  100 105 110
- Asp Asp Pro Arg Leu Glu Lys Leu Trp His Lys Ala Lys Thr Ser Gly 115 120 125
- Lys Phe Ser Gly Glu Glu Leu Asp Lys Leu Trp Arg Glu Phe Leu His 130 135 140
- His Lys Glu Lys Val His Glu Tyr Asn Val Leu Leu Glu Thr Leu Ser 145 150 155 160

Arg Thr Glu Glu Ile His Glu Asn Val Ile Ser Pro Ser Asp Leu Ser 165 170 175

Asp Ile Lys Gly Ser Val Leu His Ser Arg His Thr Glu Leu Lys Glu 180 185 190

Lys Leu Arg Ser Ile Asn Gln Gly Leu Asp Arg Leu Arg Arg Val Ser 195 200 205

His Gln Gly Tyr Ser Thr Glu Ala Glu Phe Glu Glu Pro Arg Val Ile 210 215 220

Asp Leu Trp Asp Leu Ala Gln Ser Ala Asn Leu Thr Asp Lys Glu Leu 225 230 235 240

Glu Ala Phe Arg Glu Glu Leu Lys His Phe Glu Ala Lys Ile Glu Lys 245 250 255

His Asn His Tyr Gln Lys Gln Leu Glu Ile Ala His Glu Lys Leu Arg 260 265 270

His Ala Glu Ser Val Gly Asp Gly Glu Arg Val Ser Arg Ser Arg Glu 275 280 285

Lys His Ala Leu Leu Glu Gly Arg Thr Lys Glu Leu Gly Tyr Thr Val 290 295 300

Lys Lys His Leu Gln Asp Leu Ser Gly Arg Ile Ser Arg Ala Arg His 305 310 315 320

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Glu Glu Ile His Glu Asn Val Ile Ser Pro Ser Asp Leu Ser Asp Ile 50 60

Lys Gly Ser Val Leu His Ser Arg His Thr Glu Leu Lys Glu Lys Leu Arg Ser Ile Asn Gln Gly Leu Asp Arg Leu Arg Arg Val Ser His Gln Gly Tyr Ser Thr Glu Ala Glu Phe Glu Glu Pro Arg Val Ile Asp Leu 100 105 Trp Asp Leu Ala Gln Ser Ala Asn Leu Thr Asp Lys Glu Leu Glu Ala 115 120 Phe Arg Glu Glu Leu Lys His Phe Glu Ala Lys Ile Glu Lys His Asn 135 His Tyr Gln Lys Gln Leu Glu Ile Ala His Glu Lys Leu Arg His Ala Glu Ser Val Gly Asp Gly Glu Arg Val Ser Arg Ser Arg Glu Lys His 165 170 Ala Leu Leu Glu Gly Arg Thr Lys Glu Leu Gly Tyr Thr Val Lys Lys His Leu Gln Asp Leu Ser Gly Arg Ile Ser Arg Ala Arg His Asn Glu 200 Leu <210> 3 <211> 33 <212> DNA <213> Artificial sequence <220> <223> Synthetic primer <400> 3 ccgcgtggat cccccaggct ggaaaagctg tgg 33 <210> 4 <211> 35 <212> DNA <213> Artificial sequence <220> <223> Synthetic primer <400> 4

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Tyr Glu Asn Leu Leu Ser Pro Ser Asp Met Thr His Ile Lys Ser Asp 50 55 60

Thr Leu Ala Ser Lys His Ser Glu Leu Lys Asp Arg Leu Arg Ser Ile 65 70 75 80

Asn Gln Gly Leu Asp Arg Leu Arg Lys Val Ser His Gln Leu Arg Pro 85 90 95

Ala Thr Glu Phe Glu Glu Pro Arg Val Ile Asp Leu Trp Asp Leu Ala 100 105 110

Gln Ser Ala Asn Phe Thr Glu Lys Glu Leu Glu Ser Phe Arg Glu Glu
115 120 125

Leu Lys His Phe Glu Ala Lys Ile Glu Lys His Asn His Tyr Gln Lys 130 135 140

Gln Leu Glu Ile Ser His Gln Lys Leu Lys His Val Glu Ser Ile Gly 145 150 155 160

Asp Pro Glu His Ile Ser Arg Asn Lys Glu Lys Tyr Val Leu Leu Glu 165 170 175

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- Lys Arg Glu Ser Gly Glu Glu Phe Arg Met Glu Lys Leu Asn Gln Leu 35 40 45
- Trp Glu Lys Ala Gln Arg Leu His Leu Pro Pro Val Arg Leu Ala Glu 50 55 60
- Leu His Ala Asp Leu Lys Ile Gln Glu Arg Asp Glu Leu Ala Trp Lys 65 70 75 80
- Lys Leu Lys Leu Asp Gly Leu Asp Glu Asp Gly Glu Lys Glu Ala Arg 85 90 . 95
- Leu Ile Arg Asn Leu Asn Val Ile Leu Ala Lys Tyr Gly Leu Asp Gly
  100 105 110
- Lys Lys Asp Ala Arg Gln Val Thr Ser Asn Ser Leu Ser Gly Thr Gln
  115 120 125
- Glu Asp Gly Leu Asp Asp Pro Arg Leu Glu Lys Leu Trp His Lys Ala 130 135 140
- Lys Thr Ser Gly Lys Phe Ser Gly Glu Glu Leu Asp Lys Leu Trp Arg 145 150 155 160
- Glu Phe Leu His His Lys Glu Lys Val His Glu Tyr Asn Val Leu Leu 165 170 175
- Glu Thr Leu Ser Arg Thr Glu Glu Ile His Glu Asn Val Ile Ser Pro 180 185 190
- Ser Asp Leu Ser Asp Ile Lys Gly Ser Val Leu His Ser Arg His Thr
  195 200 205

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460

Met Glu Thr Glu Asn Arg Leu His Phe Thr Ile Lys Asp Pro Ala Asn

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	610		Ile			615			•		620				
625			Gln		630					635					640
				645					650					655	
			Thr 660					665					670		
		675	Val				680					685			
	690		Phe His		-	695	_			_	700				
705	Jiu	Leu	1113	GIII	710	GIY	arg	rra	тут	715	MEC	116	vaı	wah	720

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- Leu Arg Tyr Ala Leu Leu Pro His Leu Tyr Thr Leu Phe His Gln Ala 980 985 990
- His Val Ala Gly Glu Thr Val Ala Arg Pro Leu Phe Leu Glu Phe Pro 995 1000 1005
- Lys Asp Ser Ser Thr Trp Thr Val Asp His Gln Leu Leu Trp Gly 1010  $\phantom{-}$  1015  $\phantom{-}$  1020
- Glu Ala Leu Leu Ile Thr Pro Val Leu Gln Ala Gly Lys Ala Glu 1025 1030 1035
- Val Thr Gly Tyr Phe Pro Leu Gly Thr Trp Tyr Asp Leu Gln Thr 1040 1045 1050
- Val Pro Ile Glu Ala Leu Gly Ser Leu Pro Pro Pro Pro Ala Ala 1055 1060 1065
- Pro Arg Glu Pro Ala Ile His' Ser Glu Gly Gln Trp Val Thr Leu 1070 1080
- Pro Ala Pro Leu Asp Thr Ile Asn Val His Leu Arg Ala Gly Tyr 1085 1090 1095
- Ile Ile Pro Leu Gln Gly Pro Gly Leu Thr Thr Thr Glu Ser Arg 1100 1105 1110
- Gln Gln Pro Met Ala Leu Ala Val Ala Leu Thr Lys Gly Gly Glu 1115 1120 1125
- Ala Arg Gly Glu Leu Phe Trp Asp Asp Gly Glu Ser Leu Glu Val 1130 1135 1140
- Leu Glu Arg Gly Ala Tyr Thr Gln Val Ile Phe Leu Ala Arg Asn 1145 1150 1155
- Asn Thr Ile Val Asn Glu Leu Val Arg Val Thr Ser Glu Gly Ala 1160 1165 1170
- Gly Leu Gln Leu Gln Lys Val Thr Val Leu Gly Val Ala Thr Ala 1175 1180 1185
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Asp Lys Glu Leu Glu Ala Phe Arg Glu Glu Leu Lys His Phe Glu Ala

265

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Val	Asp	Ala 355	Ala	Arg	Ala	Leu	Trp 360	Pro	Leu	Arg	Arg	Phe 365	Trp	Arg	Ser
Thr	Gly 370	Phe	Cys	Pro	Pro	Leu 375	Pro	His	Ser	Gln	Ala 380	Asp	Gln	Tyr	Val
Leu 385	Ser	Trp	Asp	Gln	Gln 390	Leu	Asn	Leu	Ala	Tyr 395	<b>Val</b>	Gly	Ala	Val	Pro 400
His	Arg	Gly	Ile	Lys 405	Gln	Val	Arg	Thr	His 410	Trp	Leu	Leu	Glu	Leu 415	Val
Thr	Thr	Arg	Gly 420	Ser	Thr	Gly	Arg	Gly 425	Leu	Ser	Tyr	Asn	Phe 430	Thr	His
Leu	Asp	Gly 435	Tyr	Leu	Asp	Leu	Leu 440	Arg	Glu	Asn	Gln	Leu 445	Leu	Pro	Gly
Phe	Glu 450	Leu	Met	Gly	Ser	Ala 455	Ser	Gly	His	Phe	Thr 460	Asp	Phe	Glu	Asp
Lys 465	Gln	Gln	Val	Phe	Glu 470	Trp	Lys	Asp	Leu	Val 475	Ser	Ser	Leu	Ala	Arg 480
Arg	Tyr	Ile	Gly	Arg 485	Tyr	Gly	Leu	Ala	His 490	Val	Ser	Lys	Trp	Asn 495	Phe
Glu	Thr	Trp	Asn 500	Glu	Pro	Asp	His	His 505	Asp	Phe	Asp	Asn	Val 510	Ser	Met
Thr	Met	Gln 515	Gly	Phe	Leu	Asn	Tyr 520	Tyr	Asp	Ala	Cys	Ser 525	Glu	Gly	Leu

Arg Ala Ala Ser Pro Ala Leu Arg Leu Gly Gly Pro Gly Asp Ser Phe 535 His Thr Pro Pro Arg Ser Pro Leu Ser Trp Gly Leu Leu Arg His Cys 555 His Asp Gly Thr Asn Phe Phe Thr Gly Glu Ala Gly Val Arg Leu Asp 570 Tyr Ile Ser Leu His Arg Lys Gly Ala Arg Ser Ser Ile Ser Ile Leu Glu Gln Glu Lys Val Val Ala Gln Gln Ile Arg Gln Leu Phe Pro Lys Phe Ala Asp Thr Pro Ile Tyr Asn Asp Glu Ala Asp Pro Leu Val Gly Trp Ser Leu Pro Gln Pro Trp Arg Ala Asp Val Thr Tyr Ala Ala Met 625 630 Val Val Lys Val Ile Ala Gln His Gln Asn Leu Leu Ala Asn Thr 645 Thr Ser Ala Phe Pro Tyr Ala Leu Leu Ser Asn Asp Asn Ala Phe Leu Ser Tyr His Pro His Pro Phe Ala Gln Arg Thr Leu Thr Ala Arg Phe 675 Gln Val Asn Asn Thr Arg Pro Pro His Val Gln Leu Leu Arg Lys Pro Val Leu Thr Ala Met Gly Leu Leu Ala Leu Leu Asp Glu Glu Gln Leu Trp Ala Glu Val Ser Gln Ala Gly Thr Val Leu Asp Ser Asn His Thr Val Gly Val Leu Ala Ser Ala His Arg Pro Gln Gly Pro Ala Asp Ala Trp Arg Ala Ala Val Leu Ile Tyr Ala Ser Asp Asp Thr Arg Ala His

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780

Pro Asn Arg Ser Val Ala Val Thr Leu Arg Leu Arg Gly Val Pro Pro

Gly 785	Pro	Gly	Leu	Val	Tyr 790	Val	Thr	Arg	Tyr	Leu 795	Asp	Asn	Gly	Leu	Cys 800		
Ser	Pro	Asp	Gly	Glu 805	Trp	Arg	Arg	Leu	Gly 810	Arg	Pro	Val	Phe	Pro 815	Thr		
Ala	Glu	Gln	Phe 820	Arg	Arg	Met	Arg	Ala 825	Ala	Glu	Asp	Pro	Val 830	Ala	Ala		
Ala	Pro	Arg 835	Pro	Leu	Pro	Ala	Gly 840	Gly	Arg	Leu	Thr	Leu 845	Arg	Pro	Ala		
Leu	Arg 850	Leu	Pro	Ser	Leu	Leu 855	Leu	Val	His	Val	Cys 860	Ala	Arg	Pro	Glu		
Lys 865	Pro	Pro	Gly	Gln	Val 870	Thr	Arg	Leu	Arg	Ala 875	Leu	Pro	Leu	Thr	Gln 880		
Gly	Gln	Leu	Val	Leu 885	Val	Trp	Ser	Asp	Glu 890	His	Val	Gly	Ser	Lys 895	Cys		
Leu	Trp	Thr	Tyr 900	Glu	Ile	Gln	Phe	Ser 905	Gln	. Asp	Gly	Lys	Ala 910	Tyr	Thr		•
Pro	Val	Ser 915	Arg	Lys	Pro	Ser	Thr 920	Phe	Asn	Leu	Phe	Val 925	Phe	Ser	Pro	٠	
Asp	Thr 930	Gly	Ala	Val	Ser	Gly 935	Ser	Tyr	Arg	Val	Arg 940	Ala	Leu	Asp	Tyr		
Trp 945	Ala	Arg	Pro	Gly.	Pro 950	Phe	Ser	Asp	Pro	Val 955	Pro	Tyr	Leu	Glu	Val 960		
Pro	Val	Pro	Arg	Gly 965	Pro	Pro	Ser	Pro	Gly 970	Asn	Pro						
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                                                                      960
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gacttgggtc tgggctatga aaccaaggag gaactgattt ttaggtactg cagcggctct
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ctggtgagtg acaaagtagg gcaggcatgt tgcagaccca tcgcctttga tgatgacctg
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ggatgtatct gatctaga
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Met Gly Gly Ser Tyr Ser Arg Glu Lys Asn Gln Pro Lys Pro Ser Pro 1 5 10 15

Lys Arg Glu Ser Gly Glu Glu Phe Arg Met Glu Lys Leu Asn Gln Leu 20 25 30

Trp Glu Lys Ala Gln Arg Leu His Leu Pro Pro Val Arg Leu Ala Glu 35 40 45

<sup>&</sup>lt;210> 11

<sup>&</sup>lt;211> 463

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Artificial sequence

<sup>&</sup>lt;220>

<sup>&</sup>lt;223> RAP-GDNF fusion sequence

<sup>&</sup>lt;400> 11

Leu	His 50	Ala	Asp	Leu	Lys	Ile 55	Gln	Glu	Arg	Asp	Glu 60	Leu	Ala	Trp	Lys
Lys 65	Leu	Lys	Leu	Asp	Gly 70	Leu	Asp	Glu	Asp	Gly 75	Glu	Lys	Glu	Ala	Arg 80
Leu	Ile	Arg	Asn	Leu 85	Asn	Val	Ile	Leu	Ala 90	Lys	Tyr	Gly	Leu	Asp 95	Gly
Lys	Lys	Asp	Ala 100	Arg	Gln	Val	Thr	Ser 105	Asn	Ser	Leu	Ser	Gly 110	Thr	Gln
Glu	Asp	Gly 115	Leu	Asp	Asp	Pro	Arg 120	Leu	Glu	Lys	Leu	Trp 125	His	Lys	Ala
Lys	Thr 130	Ser	Gly	Lys	Phe	Ser 135	Gly	Glu	Glu	Leu	Asp 140	Lys	Leu	Trp	Arg
Glu 145	Phe	Leu	His	His	Lys 150	Glu	Lys	Val	His	Glu 155	Tyr	Asn	Val	Leu	Leu 160
Glu	Thr	Leu	Ser	Arg 165	Thr	Glu	Glu	Ile	His 170	Glu	Asn	Val	Ile	Ser 175	Pro
Ser	Asp	Leu	Ser 180	Asp	Ile	Lys	Gly	Ser 185	Val	Leu	His	Ser	Arg 190	His	Thr
Glu	Leu	Lys 195		Lys	Leu	Arg	Ser 200	Ile	Asn	Gln	Gly	Leu 205	Asp	Arg	Leu
Arg	Arg 210	Val	Ser	His	Gln	Gly 215	Tyr	Ser	Thr		Ala 220	Glu	Phe	Glu	Glu
Pro	Arg	Val	Ile	Asp	Leu	Trp	Asp	Leu	Ala	Gln	Ser	Ala	Asn	Leu	Thr

Asp Lys Glu Leu Glu Ala Phe Arg Glu Glu Leu Lys His Phe Glu Ala

230

225

Lys Ile Glu Lys His Asn His Tyr Gln Lys Gln Leu Glu Ile Ala His 260 265 270

Glu Lys Leu Arg His Ala Glu Ser Val Gly Asp Gly Glu Arg Val Ser  $275 \\ 280 \\ 285$ 

Arg Ser Arg Glu Lys His Ala Leu Leu Glu Gly Arg Thr Lys Glu Leu 290 295 300

	Ly 05	Tyr	Thr	Val	Lys	Lys 310	His	Leu	Gln	Asp	Leu 315	Ser	Gly	Arg	Ile	Ser 320		
A	rg	Ala	Arg	Ala	Glu 325	Ala	Glu	Thr	Gly	Ser 330	Pro	Asp	Lys	Gln	Met 335	Ala		
Vá	al	Leu	Pro	Arg 340	Arg	Glu	Arg	Asn	Arg 345	Gln	Ala	Ala	Ala	Ala 350	Asn	Pro		
G:	lu	Asn	Ser 355	Arg	Gly	Lys	Gly	Arg 360	Arg	Gly	Gln	Arg	Gly 365	Lys	Asn	Arg		
G	ly	Cys 370	Val	Leu	Thr	Ala	Ile 375	His	Leu	Asn	Val	Thr 380	Asp	Leu	Gly	Leu		
	ly 85	Tyr	Glu	Thr	Lys	Glu 390	Glu	Leu	Ile	Phe	Arg 395	Tyr	Cys	Ser	Gly	Ser 400		
C:	ys	Asp	Ala	Ala	Glu 405	Thr	Thr	Tyr	Asp	Lys 410	Ile	Leu	Lys	Aşn	Leu 415	Ser		
A:	rg	Asn	Arg	Arg 420	Leu	Val	Ser	Asp	Lys 425	Val	Gly	Gln	Ala	Cys 430	Cys	Arg		
P	ro	Ile	Ala 435	Phe	Asp	Asp	Asp	Leu 440	Ser	Phe	Leu	Asp	Asp 445	Asn	Leu	Val	•	• •
T	yr	His 450	Ile	Leu	Arg	Lys	His 455	Ser	Ala	Lys	Arg	Cys 460	Gly	Cys	Ile			•
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	220 223		Syntl	heti	c pr	imer												
	400 cga		12 gat (	ccta	ctcg	cg gg	gagaa	agaa	c ca	gece	aagc	cgt	ccc	ga				49
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	400 cga		13 acc q	ggtt	tctg	cc to	cggcg	gcga	g cto	ctgg	agat	cct	gccg	gac a	aggto	cct		57

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Gly Lys Tyr Ser Arg Glu Lys Asn Gln Pro Lys Pro Ser Pro Lys Arg
Glu Ser Gly Glu Glu Phe Arg Met Glu Lys Leu Asn Gln Leu Trp Glu
    50
                       55
Lys Ala Gln Arg Leu His Leu Pro Pro Val Arg Leu Ala Glu Leu His
Ala Asp Leu Lys Ile Gln Glu Arg Asp Glu Leu Ala Trp Lys Lys Leu
                85
Lys Leu Asp Gly Leu Asp Glu Asp Gly Glu Lys Glu Ala Arg Leu Ile
Arg Asn Leu Asn Val Ile Leu Ala Lys Tyr Gly Leu Asp Gly Lys Lys
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Asp Ala Arg Gln Val Thr Ser Asn Ser Leu Ser Gly Thr Gln Glu Asp

Gly Leu Asp Asp Pro Arg Leu Glu Lys Leu Trp His Lys Ala Lys Thr Ser Gly Lys Phe Ser Gly Glu Glu Leu Asp Lys Leu Trp Arg Glu Phe Leu His His Lys Glu Lys Val His Glu Tyr Asn Val Leu Leu Glu Thr 180 185 Leu Ser Arg Thr Glu Glu Ile His Glu Asn Val Ile Ser Pro Ser Asp 195 200 Leu Ser Asp Ile Lys Gly Ser Val Leu His Ser Arg His Thr Glu Leu 210 215 220 Lys Glu Lys Leu Arg Ser Ile Asn Gln Gly Leu Asp Arg Leu Arg Arg Val Ser His Gln Gly Tyr Ser Thr Glu Ala Glu Phe Glu Glu Pro Arg 245 250 Val Ile Asp Leu Trp Asp Leu Ala Gln Ser Ala Asn Leu Thr Asp Lys Glu Leu Glu Ala Phe Arg Glu Glu Leu Lys His Phe Glu Ala Lys Ile Glu Lys His Asn His Tyr Gln Lys Gln Leu Glu Ile Ala His Glu Lys 290 295 Leu Arg His Ala Glu Ser Val Gly Asp Gly Glu Arg Val Ser Arg Ser 305 310 315 Arg Glu Lys His Ala Leu Leu Glu Gly Arg Thr Lys Glu Leu Gly Tyr 325 Thr Val Lys Lys His Leu Gln Asp Leu Ser Gly Arg Ile Ser Arg Ala 340 345

....

Arg His Asn Glu Leu 355

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Arg	Lys	Met	Ala 20	Pro	Arg	Arg	Glu	Arg 25	Val	Ser	Thr	Leu	Pro 30	Arg	Leu
Gln	Leu	Leu 35	Val	Leu	Leu	Leu	Leu 40	Pro	Leu	Met	Leu	Val 45	Pro	Gln	Pro
Ile	Ala 50	Gly	His	Gly	Gly	Lys 55	Tyr	Ser	Arg	Glu	Lys 60	Asn	Glu	Pro	Glu
Met 65	Ala	Ala	Lys	Arg	Glu 70	Ser	Gly	Glu	Glu	Phe 75	Arg	Met	Glu	Lys	Leu 80
Asn	Gln	Leu	Trp	Glu 85	Lys	Ala	Lys	Arg	Leu 90	His	Leu	Ser	Pro	Val 95	Arg
Leu	Ala	Glu	Leu 100	His	Ser	Asp	Leu	Lys 105	Ile	Gln	Glu 、	Arg	Asp 1:10	Glu	Leu
Asn	Trp	Lys 115	Lys	Leu	Lys	Val	Glu 120	Gly	Leu	Asp	Lys	Asp 125	Gly	Glu	Lys
Glu	Ala 130	Lys	Leu	Ile	His	Asn 135	Leu	Asn	Val	Ile	Leu 140	Ala	Arg	Tyr	Gly
Leu 145	Asp	Gly	Arg	Lys	Asp 150	Ala	Gln	Met	Val	His 155	Ser	Asn	Ala	Leu	Asn 160
Glu	Asp	Thr	Gln	Asp 165		Leu	Gly	Asp	Pro 170	Arg	Leu	Glu	Lys	Leu 175	Trp
His	Lys		Lys 180		Ser	Gly	Lys	Phe 185		Ser	Glu		Leu 190	_	Lys
Leu	Trp	Arg 195	Glu	Phe	Leu	His	Tyr 200	Lys	Glu	Lys	Ile	Gln 205	Glu	Tyr	Asn
Val	Leu 210	Leu	Asp	Thr	Leu	Ser 215	Arg	Ala	Glu	Glu	Gly 220	Tyr	Glu	Asn	Leu
Leu 225	Ser	Pro	Ser	Asp	Met 230	Ala	His	Ile	Lys	Ser 235	Asp	Thr	Leu	Ile	Ser 240

Lys His Ser Glu Leu Lys Asp Arg Leu Arg Ser Ile Asn Gln Gly Leu 245 250 255

Asp Arg Leu Arg Lys Val Ser His Gln Gly Tyr Gly Ser Thr Thr Glu 260 265 270

Phe Glu Glu Pro Arg Val Ile Asp Leu Trp Asp Leu Ala Gln Ser Ala 275 280 285

Asn Phe Thr Glu Lys Glu Leu Glu Ser Phe Arg Glu Glu Leu Lys His 290 295 300

Phe Glu Ala Lys Ile Glu Lys His Asn His Tyr Gln Lys Gln Leu Glu 305 310 315 320

Ile Ser His Gln Lys Leu Lys His Val Glu Ser Ile Gly Asp Pro Glu 325 330 335

His Ile Ser Arg Asn Lys Glu Lys Tyr Val Leu Leu Glu Glu Lys Thr 340 345 350

Lys Glu Leu Gly Tyr Lys Val Lys Lys His Leu Gln Asp Leu Ser Ser 355 360 365

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<213> Rat

<400> 23

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Gly Lys Tyr Ser Arg Glu Lys Asn Glu Pro Glu Met Ala Ala Lys Arg 35 40 45

Glu Ser Gly Glu Glu Phe Arg Met Glu Lys Leu Asn Gln Leu Trp Glu 50 55 60

Lys Ala Lys Arg Leu His Leu Ser Pro Val Arg Leu Ala Glu Leu His 65 70 75 80

Ser Asp Leu Lys Ile Gln Glu Arg Asp Glu Leu Asn Trp Lys Lys Leu 85 90 95 Lys Val Glu Gly Leu Asp Gly Asp Gly Glu Lys Glu Ala Lys Leu Val 105 His Asn Leu Asn Val Ile Leu Ala Arg Tyr Gly Leu Asp Gly Arg Lys Asp Thr Gln Thr Val His Ser Asn Ala Leu Asn Glu Asp Thr Gln Asp 135 Glu Leu Gly Asp Pro Arg Leu Glu Lys Leu Trp His Lys Ala Lys Thr Ser Gly Lys Phe Ser Ser Glu Glu Leu Asp Lys Leu Trp Arg Glu Phe Leu His Tyr Lys Glu Lys Ile His Glu Tyr Asn Val Leu Leu Asp Thr Leu Ser Arg Ala Glu Glu Gly Tyr Glu Asn Leu Leu Ser Pro Ser Asp 195 200 Met Thr His Ile Lys Ser Asp Thr Leu Ala Ser Lys His Ser Glu Leu 210 Lys Asp Arg Leu Arg Ser Ile Asn Gln Gly Leu Asp Arg Leu Arg Lys Val Ser His Gln Gly Tyr Gly Pro Ala Thr Glu Phe Glu Glu Pro Arg Val Ile Asp Leu Trp Asp Leu Ala Gln Ser Ala Asn Phe Thr Glu Lys Glu Leu Glu Ser Phe Arg Glu Glu Leu Lys His Phe Glu Ala Lys Ile Glu Lys His Asn His Tyr Gln Lys Gln Leu Glu Ile Ser His Gln Lys Leu Lys His Val Glu Ser Ile Gly Asp Pro Glu His Ile Ser Arg Asn 310 315 Lys Glu Lys Tyr Val Leu Leu Glu Glu Lys Thr Lys Glu Leu Gly Tyr

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Lys Val Lys Lys His Leu Gln Asp Leu Ser Ser Arg Val Ser Arg Ala

Arg His Asn Glu Leu 355

<210> 24

<211> 348

<212> PRT

<213> Chicken

<400> 24

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Val Ser Thr Arg Ala Ser Lys Tyr Thr Arg Glu Ala Asn Glu Gly Leu 20 25 30

Ala Asp Ala Lys Arg Glu Ala Gly Glu Phe Arg Val Val Arg Leu 35 40 45

Asn Gln Val Trp Glu Lys Ala Gln Arg Leu Gln Leu Ser Ala Val Lys 50 55 60

Leu Ala Glu Leu His Ser Asp Leu Lys Ile Gln Glu Lys Asp Glu Leu 65 70 75 80

Ser Trp Lys Lys Leu Lys Ala Glu Gly Leu Gly Glu Asp Gly Glu Lys 85 90 95

Glu Ala Lys Leu Arg Arg Asn Ile Asn Val Ile Met Thr Lys Tyr Gly
100 105 110

Met Asn Gly Lys Lys Asp Ser His Leu Thr Asp Thr Asn Tyr Ile Lys 115 120 125

Asp Gly Thr Glu Ser Asp Thr Leu Asp Asp Pro Arg Leu Glu Lys Leu 130 135 140

Trp Ser Lys Ala Lys Thr Ser Gly Lys Phe Ser Asp Glu Glu Leu Asp 145 150 155 160

Lys Leu Trp Arg Glu Phe Lys His His Lys Glu Lys Ile Arg Glu Tyr 165 170 175

Asn Ile Leu Leu Glu Thr Val Ser Arg Thr Glu Asp Ile His Lys Lys 180 185 190

Val Ile Asn Pro Ser Glu Glu Asn Pro Val Lys Glu Glu Val Leu His 195 200 205 Asn Lys His Arg Glu Leu Lys Glu Lys Leu Arg Ser Ile Asn Gln Gly 210 Phe Glu Arg Leu Arg Lys Val Ser His Gln Gly Tyr Asp Ala Thr Ser Glu Phe Glu Glu Pro Arg Val Ile Asp Leu Trp Asp Met Ala Lys Ser Ala Asn Phe Thr Glu Lys Glu Leu Glu Ser Phe Arg Glu Glu Leu Lys His Phe Glu Ala Lys Ile Glu Lys His His His Tyr Gln Lys Gln Leu Glu Ile Ser His Glu Lys Leu Lys His Ile Glu Gly Thr Gly Asp Lys 295 Glu His Leu Asn Arg Asn Arg Glu Lys Tyr Ala Met Leu Glu Glu Lys Thr Lys Glu Leu Gly Tyr Lys Val Lys Lys His Leu Gln Asp Leu Ser 325 330 Ser Arg Ile Ser Gln Gly Leu Gln His Asn Glu Leu 340 <210> 25 <211> 331 <212> PRT <213> Zebrafish <400> 25 Met Ala Gly Lys Tyr Ser Lys Glu Met Asn Glu Lys Asn Ala Ser Asp Lys Ser Asn Asn Gln Val Glu Phe Arg Ile Ala Lys Leu Asn Gln Val Trp Glu Lys Ala Ile Arg Met Gln Leu Ala Pro Val Arg Leu Ser Glu 35 40 Leu His Ser Asp Leu Lys Ile Gln Glu Lys Asp Glu Leu Gln Trp Lys

75

Lys Leu Lys Ala Glu Gly Met Asp Glu Asp Gly Glu Arg Glu Ala Lys

Leu	Arg	Arg	ASII	85	ASII	iie	116	reu	90	гуѕ	Tyr	GIY	мес	95	GIY
Lys	Lys	Asp	Thr 100	Arg	Thr	Leu	Asp	Ser 105	Asn	Arg	Leu	Lys	Asp 110	His	Glu
Val	Lys	Ile 115	Gly	Asp	Thr	Phe	Asp 120	Asp	Pro	Lys	Leu	Asp 125	Lys	Leu	Trp
Asn	Lys 130	Ala	Arg	Thr	Ser	Gly 135	Lys	Phe	Ser	Asp	Glu 140	Glu	Leu	Gln	Thr
Leu 145	His	Arg	Glu	Phe	Gln 150	His	His	Lys	Asp	Lys 155	Ile	His	Glu	Tyr	Asn 160
Ile	Val	Met	Asp	Thr 165	Val	Ser	Arg	Thr	Glu 170	Glu	Ile	His	Lys	Asn 175	Val
Ile	Ser	Pro	Leu 180	Glu	Gly	Asp	Val	Lys 185	Glu	Asn	Val	Leu	His 190	Gln	Lys
His	Thr	Asp <sup>-</sup> 195	Leu	Lys.	Gln	Arg	Met 200	Arg	Asp	Leu	Asn	Gln 205	Gly	Phe	Glu
Arg	Leu 210	Arg	Lys	Ile	Thr	His 215	Glu	Gly	Tyr	Thr	Asp 220	Asp	Ser	Glu	Phe
Arg 225	Glu	Pro	Arg	Val	Ile 230	Glu	Leu	Trp	Glu	Met 235	Ala	Lys	Arg	Ser	Asn 240
Leu	Ser	Glu	Asp	Glu 245	Leu	Asp	Ser	Leu	Lys 250	Glu	Glu	Leu	Arg	His 255	Phe
Glu	Thr	Lys	Val 260	Glu	Lys		Gln		_	Gln	Glu	Gln	Leu 270	Glu	Leu
Ser	His	Gln 275	Lys	Leu	Lys	His	Val 280	Glu	Ala	Leu	Gly	Asp 285	Glu	Asp	His
Ile	Met 290	Arg	Asn	Lys	Glu	Lys 295	Tyr	Asn	Thr	Leu	Ala 300	Glu	Lys	Ala	Arg
305					310		Lys			315	Asp	Leu	Thr	Asn	Lys 320
Leu	Ser	Lys	Asn	Gly	Leu	Gln	His	Asn	Glu	Leu					

<210> 26

<211> 379

<212> PRT

<213> Fruit fly

<400> 26

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Ile Ala Leu Gln Gly Val Asp Ala Asp Lys Lys Gln Ser Lys Lys Tyr
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Ser Lys Glu Ala Asn Asp Pro His Phe Gln Gln Val Lys Gln Glu Lys
35 40 45

Tyr Asp Pro Asp Phe Lys Ser Ile Gln Arg Pro Phe Arg Met Ala Lys 50 55 60

Leu Asn Leu Val Trp Ala Lys Ala Gln Asn Arg Leu Thr Glu Pro Lys 65 70 75 80

Leu Lys Ser Leu Tyr Met Glu Leu Lys Ile His Asp Lys Glu Glu Ile 85 90 95

Ala Trp Lys Gln Leu Asn Ser Gln His Lys Asp Lys Asp Gly Leu Lys
100 105 110

Ala Asp Glu Leu Arg Arg Lys Leu Ile Gly Ile Met Ser Ser Tyr Asp 115 120 125

Leu Leu Glu His Phe Asp Asp Thr Gln Asp Thr Glu Lys Leu Lys Pro 130 135 140

Tyr Lys Lys Phe His Asp Ala Glu Glu Arg His Arg Asn Lys Ser Leu 145 150 155 160

Phe Lys Asp Lys Leu Asn Arg Leu Trp Glu Lys Ala Glu Ile Ser 165 170 175

Gly Phe Thr Ala Glu Glu Leu Lys Ser Leu Lys Gln Glu Phe Asp His 180 185 190

His Gln Asp Lys Val Asp Val Tyr Tyr Ser Leu Leu Glu Asn Ile Gly
195 200 . 205

Thr Val Asp Thr Asp Lys His Glu Asn Ala Ile Asn Thr Glu Asp Leu 210 215 220

Asp Thr Tyr Asn Leu Ile Ser Asn Asp Val Asn Glu Asn Asp Ile Lys 230 235 Thr His Ala Gln Asn Val Lys Ser Phe Glu Asn Asp Leu Asn Thr Leu 250 Arg Gly His His Thr Gly Ile Lys Asp His Tyr Asp Arg Leu Glu Arg 265 Leu Val Ser Ser Gly Pro His Ser Gln Asp Phe Ile Glu Pro Lys Val Gln Gly Leu Trp Arg Val Ala Gln Ala Ser Asn Phe Thr Val Lys Glu Leu Glu Ser Ile Lys Thr Glu Leu His His Phe Glu Ser Arg Leu Leu Lys Leu Arg His Leu His Ala Glu His Ala Leu Gln Lys Glu Lys Tyr 325 Lys Gly Glu Lys Val Lys Asp Lys Ser Ser Arg Phe Glu Glu Met Glu Asp Gln Leu Lys Lys Gln Thr Arg Lys Val Glu Lys Leu Gln Glu Asn Ile Glu Lys Thr Ile Phe Lys His Thr Glu Leu <210> 27 <211> 400 <212> PRT <213> Mosquito Glu Leu Cys Pro Ile Ala Arg Arg Lys Arg Gly Ile Lys His Thr Leu Thr Met Pro Leu Phe Thr Arg Leu Cys Val Ile Val Phe Thr Val Leu 20 30 Val Cys Asn His Val Val Gln Ser Glu Lys Ala His Ser Lys Tyr Ser Lys His Ala Asn Ala Leu Pro Asp Ser Glu Ile Tyr Glu Pro Asp Phe

.

60

55

65	ASII	116	GIII	AIG	70	PHE	Arg	Met	Ala	75	Leu	ASII	ьеи	Val	80 80
Thr	Lys	Ala	Gln	His 85	Arg	Leu	Thr	Glu	Pro 90	Lys	Leu	Lys	Ser	Leu 95	Tyr
Thr	Glu	Leu	Lys 100	Leu	His	Asp	Lys	Glu 105	Glu	Leu	Thr	Tyr	Lys 110	Gln	Leu
Lys	Glu	Lys 115	Asp	Lys	Asp	Gly	Leu 120	Lys	Glu	Ala	Glu	Leu 125	Arg	Asn	Lys
Leu	Val 130	Ser	Ile	Met	Ser	Thr 135	Tyr	Gly	Leu	Leu	Glu 140	His	Phe	Asp	Asp
Thr 145	Gln	Asp	Pro	Glu	Lys 150	Tyr	Lys	Leu	Ala	Lys 155	Ser	Ser	Asp	Gly	Ala 160
Pro	Lys	Lys	Asp	Thr 165	Tyr	Lys	Asn	Lys	Ser 170	Leu	Phe	Lys	Asp	Lys 175	Lys
Leu ,	Asn	Lys	Leu 180	Trp	Asp	Lys	Ala	Glu 185	Ser	Ala	Gly	Phe	Thr 190	Lys	Gľu
Glu	Leu	Asp 195	Ala	Leu	Arg	Glu	Glu 200	Phe	·Asp	His	His	Gln 205	Ala	Lys	Ile
Asp	Val 210	Tyr	Tyr	Ser	Leu	Leu 215	Glu	Arg	Leu	Gly	Asp 220	Asp	Asp	Asp	Gly
Gly 225	Ala	Ala	Gly	Gln	Gly 230	Ser	Arg	Arg	Asp	Asp 235	Asp	Ala	Leu	Leu	Asn 240
Ala	Val	Asn	Asp	Glu 245		His	Asp	_	Tyr 250		Glu	Val	Asp	Arg 255	Ala
Glu	Glu	Thr	Asp 260	Arg	Ser	Gln	Pro	Gly 265	Ala	Asn	Lys	Gln	His 270	Ala	Tyr
Leu	His	Lys 275	Ser	Asn	Gln	Leu	Arg 280	Glu	Lys	His	Arg	Glu 285	Ile	Arg	Asp
Asn	Phe 290	Asp	Arg	Leu	Asp	Arg 295	Ile	Ala	Ser	Lys	Gly 300	Pro	Lys	Ser	Gln
Asp 305	Phe	Val	Glu	Pro	Lys 310	Val	Gln	Gly	Leu	Trp	Arg	Val	Ala	Leu	Ala 320

Ser Asp Phe Ser Ala Asp Glu Leu Ala Ser Leu Lys Val Glu Leu Leu 325 330 335

His Tyr Glu Ser Arg Leu Leu Lys Leu Arg His Met His Ala Glu His 340 345 350

Ala Leu Ser Leu Glu Lys His Lys His Ser Asp Ala Lys Ala Asp Thr 355 360 365

His Lys Leu Met Glu Asp Asn Ile Lys Lys Gln Thr Arg Lys Val Glu 370 380

Lys Met Glu Glu Val Glu Arg Arg Ile Phe Lys His Ser Glu Leu 385 390 395 400

<210> 28

<211> 331

<212> PRT

<213> Flatworm

<400> 28

Met Arg Asn His Phe Ser Phe Leu Leu Phe Leu Leu Val Ile Gly Ser 1 5 10 15

Ala His Asn Lys Lys Thr Gln Tyr Arg Thr Glu Arg Ile Asn Phe Ile
20 25 30

Tyr Glu Lys Ala Leu Gln His Val Thr Asp Arg Gln Asn Leu Ala Arg 35 40 45

Leu Glu Lys Glu Leu Ser Gly Tyr Asp Ala Ile Tyr Leu Ala Ser Lys 50 55 60

Ser Asn Arg Gln Gly Thr Gln Gly Thr Lys Glu Ile Asp Lys Ile Asp 65 70 75 80

Asp Lys Leu Gly Lys Ile Leu Glu Lys Tyr Gly Leu Glu Lys Ala Val 85 90 95

Leu Ala Phe Lys Glu Lys Tyr Lys His Lys Asn Leu Phe Gln Gln Thr
100 105 110

Asp Asp Asn Glu Pro Leu Pro Ser Gly Lys Phe Thr Asp Gln Asn Leu 115 120 125

Gln Lys Leu Trp Ser Gln Ala Gln Asn Gly Lys Phe Ser Gln Lys Glu 130 135 140

Leu 145	Asn	Ala	Leu	His	Gly 150	Glu	Leu	Lys	Glu	Val 155	Glu	Gln	Lys	Met	Arg 160
Val	Tyr	Glu	Asp	Gln 165	Leu	Asp	Asp	Phe	Lys 170	Lys	Val	Pro	His	Glu 175	Asn
Ser	Ile	Gln	His 180	Asp	Ile	Glu	Ser	Ile 185	Gly	Asp	Lys	Thr	Lys 190	Lys	Leu
Lys	Ala	Ala 195	Asn	Arg	Glu	Leu	Asn 200	Asp	His	Leu	Asp	Glu 205	Val	His	Arg
Lys	Val 210	Thr	Ser	Glu	Glu	Phe 215	Ser	Pro	Phe	Asn	Glu 220	Pro	Arg	Val	Lys
Arg 225	Leu	Trp	Lys	Leu	Ala 230	Gln	Glu	Asn	Glu	Lys 235	Leu	Thr	Pro	His	Glu 240
Leu	Ser	Val	Leu	Lys 245	Asp	Glu	Leu	Ser	His 250	Phe	Glu	Ser	Gln	Leu 255	Lys
Lys	Ile	Glu	Phe 260	His	Lys	Val	Phe	Phe 265	Phe	Val	Ala	Asņ	Ser 270	Cys	Pro
Lys	Arg	Gly 275	Lys	Asn	Glu	Glu	Val 280	Ser	Arg	Leu	Gln	Glu 285	Asp	Ala	Glu
Glu	Arg 290	Gly	Lys	Asp	Lys	Ser 295	Gln	Val	Tyr	Glu	Asn 300	Leu	Glu	Leu	Ser
Ile 305	Lys	His	Glu	Lys	Leu 310	Asn	Arg	Lys	Ala	Arg 315	Lys	Leu	Glu	Lys	Tyr 320
Ile	Glu	Glu	Lys	Ile 325	Ile	Ile	His	Arg	Glu 330	Leu					